1, wherein said heparinase enzyme is expressed from a recombinant nucleotide sequence, in *Escherichia coli* or *Flavobacterium heparinum.* Applicants respectfully submit that the Applicants respectfully submit that this amendment does not modify the scope of the claims, but is made to clarify that the heparinase enzyme may be expressed recombinantly in *Escherichia coli* or *Flavobacterium heparinum.* Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 102(e)

Claims 1-5 and 18-19 are rejected under 35 USC §102 (e) as allegedly being anticipated by U.S. Patent No. 5,567,417 ("the '417 patent"). The Office Action states that the '417 patent describes a method of decreasing localized inflammatory responses arising from an ischemia/reperfusion injury in a tissue via topical application or implantation with an effective dosage of heparinase. Applicants respectfully traverse the rejection.

"To anticipate a claim, a prior art reference must disclose every limitation of the claimed invention, either explicitly or inherently." *In re Schreiber*, 128 F.3d 1473, 1477, 44 U.S.P.Q.2D 429, 1431 (Fed. Cir. 1997). Applicants respectfully submit that each and every element of independent claim 1 has not been met by the '417 reference. Claim 1 recites a method to decrease localized inflammatory responses arising from an ischemia/reperfusion injury in a tissue of a patient comprising intravascularly administering heparinase. The Office Action admits that intravascular administration is not described in the '417 patent. In particular, it is stated that "it would have been well within the purview of one of ordinary skill in the art at the time the invention was made to design an intravascular solution of heparinase enzyme to decrease localized inflammation arising from an ischemia/reperfusion injury." (Office Action at 3.) However, this purported suggestion to design an intravascular solution is insufficient to

anticipate the claims, which recite intravascularly administration of heparinase. Accordingly, Applicants respectfully submit that the '417 patent does not teach each and every element under §102(e) of independent claim 1 and dependent claims 2-5 and 18-19. The anticipation rejection is improper and withdrawal thereof is respectfully requested.

However, if it was intended that the rejection be based on obviousness pursuant to §103 instead, Applicants maintain that the '417 patent does not teach or suggest the claimed invention. Applicants submit that such an obviousness rejection based on '417 patent is improper because (1) the '417 patent does not describe intravascular administration of the heparinase; (2) the '417 patent is only directed to applying heparinase to inhibit angiogenesis, the function of which is contrary to the angiogenic function involved in wound healing and acts as a separate and distinct function from inflammation; and (3) there is no reasonable expectation that the inhibition of angiogenesis or neovascularization would inherently promote inflammation.

The '417 patent describes topically applying heparinase to inhibit neovascularization. The '417 patent does not teach or suggest the intravascular administration of heparinase to a patient to decrease localized inflammatory responses arising from ischemia/reperfusion injury in a tissue. The '417 patent describes "[s]olutions or suspensions used for parenteral, intradermal, subcutaneous, or topical application," but does not teach or suggest intravascular adminstration. The Office Action does not provide a reason why intravascular administration is obvious over these other modes of administration.

Applicants' specification, on the other hand, demonstrated in Example 7, pages 35-39 of the specification, that intravascular administration of heparinase enzyme will decrease neutrophil adhesion and transmigration through activated endothelium and basement membrane of the vasculature subsequent to an ischemic event thereby decreasing the localized inflammatory

response which would have otherwise arisen from an ischemia/reperfusion injury to tissue. Specifically, in this example intravital video microscopy was used to quantitate neutrophil movement through the vasculature after an ischemic event in rats, and neutrophil movement in untreated rats was compared with that in heparinase treated rats. As described in the specification, pages 38, line 28 through 39, line 8 and shown in Figures 12-14, in untreated rats the number of leukocytes which adhered to the endothelial walls of the vasculature and extravasated progressively increased during reperfusion, but in heparinase treated rats no significant difference was observed for either leukocyte adhesion or extravasation when compared to control animals which had not been subject to an ischemic event. Applicants respectfully submit that nothing in the '417 patent suggests that intravascular administration of heparinase would result in the localized reduction of inflammation in patients, as described in the instant specification.

Moreover, the Office Action states that the '417 patent describes "a method of decreasing localized inflammatory responses arising from an ischemia/reperfusion injury (i.e. wound repair) in a tissue of a patient." (Office Action at 3.) Applicants respectfully disagree. The '417 patent describes the inhibition of angiogenesis, not the promotion of wound repair or the reduction of inflammation, as alleged. Angiogenesis, as described in the '417 patent, is ". . . a fundamental process by which new blood vessels are formed . . . . It is essential in reproduction, development and wound repair." The '417 patentees discuss the problems associated with unregulated angiogenesis:

> In arthritis, new capillaries invade the joint and destroy cartillage. In diabetes, new capillaries invade the vitreous, bleed, and cause blindness. Ocular neovascularization is the most common cause of blindness. Tumor growth and metastasis are angiogenesis-dependent. A tumor must continuously stimulate the growth of new capillary blood vessels for the tumor itself to grow. (Col. 1, lines 20-27.)

The '417 patentees therefore seek to inhibit unregulated angiogenesis; they do not seek to promote wound healing.

In Applicants' own U.S. Patent No. 5,997,863, Applicants describe the distinction between wound healing and the reduction of inflammation: "The wound healing process is generally divided into three temporally overlapping phases: inflammation, proliferation and remodeling." (Col. 2, lines 60-62.) "Angiogenesis, the formation of new blood vessels in response to chemoattractant and angiogenic signals . . . , and fibroplasia, the accumulation of fibroblasts and formation of granulation tissue, also occurs during the proliferative stage." (Col. 3, lines 12-17.) Therefore, inflammation and angiogenesis are two completely separate stages involved in wound healing.

The patentees of the '417 patent sought to inhibit one phase of wound healing, the proliferation stage, to stop the unregulated development of new blood vessels. Accordingly, contrary to the Examiner's contention, the '417 patent method seeks to stop wound healing at the proliferative stage, not promote it. The '417 patent therefore teaches away from the present invention and does render the claims obvious.

Nevertheless, insofar as the Examiner may maintain that the '417 patent describes wound healing and that any application of heparinase would render the claimed invention anticipated by inherency, Applicants respectfully disagree. Wound healing (as stated in the Office Action) and the reduction of an inflammatory response cannot be equated. Inflammation is a cascade of

events that occur in response to injury or infection. Normally, wound healing is a sequel to inflammation, occurring in the days to weeks following an injury.

Inflammation and wound healing can be distinguished from one another by three primary factors: 1) time, 2) primary type of cells involved and 3) key humoral factors. Inflammation begins almost immediately upon injury, and typically peaks within 24 to 48 hrs. The primary cells involved in the inflammatory response, are endothelial cells lining the blood vessels and neutrophils and other blood leukocytes. Injury to tissue and blood vessels, causes the release of chemotactic factors (C5a, Il-8, PAF), cytokines (Il-1, TNFα) and oxygen radicals (OH, HOCL, O_2^-) from the injured tissue and endothelial cells which line the blood vessels. The release of these humoral factors, triggers the increased expression of adhesion molecules (selectins, integrins) on the endothelial cell surface. Increased adhesion molecules on endothelium, along with chemokines, promote the activation of neutrophils. Activated neutrophils adhere to endothelial cells, then migrate from blood into tissue and secrete proteolytic enzymes, cytokines, chemotactic factors, and oxygen radicals, which injure and kill cells composing the tissue. The release of these substances by neutrophils in the tissue is the primary event responsible for cell death in tissues following injury. An example of tissue injury which results from an inflammatory reaction, is necrotic, nonfunctional myocardium following ischemic injury to the heart. *See, e.g.,* Frangogiannis, NG, Smith CW, and Entman ML, "The inflammatory response in myocardial infarction," *Cardiovascular Res.*, 53:31-47 (2002)(Exhibit A) and Hayward R, Nossuli TO and Lefer AM. Heparinase III exerts endothelial and cardioprotective effects in feline myocardial ischemia-reprefusion injury. *J Pharmacol. Exper. Therap.* 263: 1032-1038 (1997)(Exhibit B).

In contrast, wound healing is the process of repairing and healing which takes place over a period of days to weeks following an injury. The key stages in wound healing, are: reepithelialization, formation of granulation tissue, neovascularization, and contraction. *See* Singer AJ and Clark RAF, "Cutaneous wound healing," *New Eng J Med.* 341: 738-746 (1999)(Exhibit C). The primary cells involved in wound healing are macrophages, epithelial cells, fibroblasts and endothelial cells. Of these different cell types, macrophages have been shown to be essential cells in each stage of the process.(Leibovich and Ross, 1975). These cells secrete a large number of cytokines, chemokines, growth factors, collagenase and other enzymes. Secretion of cytokines by macrophages, increases the concentration of growth factors in the wound, by stimulating production of growth factors by cells in the surrounding tissue. Collagenase is vital to allowing new epithelial cells to migrate to cover the wound. The degradation of extracellular matrix proteins by macrophages, also frees up a variety of growth factors(PDGF, EGF, KGF, TGFα, VEGF) bound to matrix, and further enhances cell proliferation and neovascularization in the wound. Finally, contraction(closure) and strengthening of the wound are enhanced by the secretion of TGFβ by macrophages which stimulates fibroblast collagen synthesis. *See, e.g.,* Mutsaers SE, Bishop JE, McGrouther G and Laurent GJ, "Mechanisms of tissue repair: wound healing to fibrosis," *Int. J. Biochem. Cell Biol.* 29: 5-17 (1997)(Exhibit D) and Singer and Clark, "Cutaneous Wound Healing," *New England J. of Med.*, 341(1): 738-746 (1999)(Exhibit C).

Accordingly, reducing inflammation is merely one phase of the wound healing process, and a reference generally teaching wound healing cannot be assumed to inherently teach the reduction of inflammation:

> Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient. If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient. In re Oelrich, 666 F.2d 578, 581, 212 U.S.P.Q. (BNA) 323, 326 (CCPA 1981) (quoting Hansgirg v. Kemmer, 26 C.C.P.A. 937, 102 F.2d 212, 214, 40 U.S.P.Q. (BNA) 665, 667 (CCPA 1939)) (internal citations omitted).

Applicants submit that the '417 patent does not even raise the possibility that heparinase may reduce inflammation because it is directed only to the inhibition of wound healing by inhibiting angiogenesis. Moreover, even if the '417 patent did teach that heparinase promotes wound healing, that would not be sufficient to establish inherency because it would only raise a probability that it acts during one of three potential phases of wound healing, inflammation, proliferation or remodeling. A probability or possibility that heparinase acts by a particular method is not sufficient to establish inherency. Accordingly, Applicants respectfully submit that the Office Action fails to establish anticipation or obviousness of the claimed invention. Withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. § 103

Claims 1 and 7 were rejected under §103 as allegedly being unpatentable over U.S. Patent No. 5,567,417 in view of U.S. Patent No. 5,714,376 ("the '376 patent").

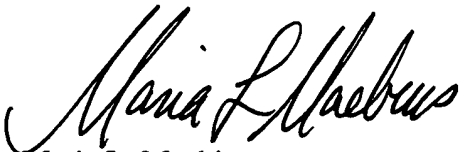
Applicants respectfully submit that the '417 patent does not render claims 1 or 7 anticipated or obvious for the reasons set forth above. In addition, the '376 patent adds nothing to remedy the deficiencies of the '417 patent. The '376 patent merely addresses the cloning of a heparinase gene from *Flavobacterium heparinum*. It does not teach or suggest a method to decrease localized inflammatory responses arising from an ischemia/reperfusion injury in a

tissue of a patient comprising intravascularly administering using the cloned heparinase. Accordingly, the combination of the '417 patent and the '376 patent does not provide a *prima facie* case of obviousness. Withdrawal of the rejection under §103 is respectfully requested.

Conclusion

Applicants respectfully submit that this Application is in condition for allowance and an expedited issuance of a Notice of Allowance is respectfully requested.

Respectfully Submitted,



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